2020

Randomized Controlled Trial of Difelikefalin for Chronic Pruritus in Hemodialysis Patients

S. Fishbane
Zucker School of Medicine at Hofstra/Northwell, sfishbane@northwell.edu

V. Mathur

M. J. Germain

S. Shirazian

S. Bhaduri

See next page for additional authors

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Randomized Controlled Trial of Difelikefalin for Chronic Pruritus in Hemodialysis Patients

Steven Fishbane[1], Vandana Mathur[2], Michael J. Germain[3], Shayan Shirazian[4], Sarbani Bhaduri[5], Catherine Munera[6], Robert H. Spencer[6] and Frédérique Menzaghi[6]; on behalf of the Trial Investigators[7]

[1]Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York, USA; [2]MathurConsulting, Woodside, California, USA; [3]Baystate Medical Center and Tufts University, Springfield, Massachusetts, USA; [4]Columbia University Medical Center, Division of Nephrology, Department of Medicine, College of Physicians and Surgeons at Columbia University, New York, New York, USA; [5]Bhaduri Biotech Consulting, El Paso, Texas, USA; and [6]Cara Therapeutics, Inc., Stamford, Connecticut, USA

Introduction: There is an unmet medical need for pruritus associated with chronic kidney disease, a distressing complication characterized by generalized and persistent itch affecting 20% to 40% of patients undergoing hemodialysis. Here we report the results of a phase 2 trial evaluating the efficacy and safety of a novel peripherally restricted kappa opioid receptor agonist, difelikefalin, in adult patients undergoing hemodialysis with pruritus.

Methods: In this study, 174 hemodialysis patients with moderate-to-severe pruritus were randomly assigned to receive difelikefalin (0.5, 1.0, or 1.5 μg/kg) or placebo intravenously thrice weekly after each hemodialysis session for 8 weeks in a double-blind, controlled trial. The primary endpoint was the change from baseline at week 8 in the weekly mean of the 24-hour Worst Itching Intensity Numerical Rating Scale score. The secondary efficacy endpoint was the change in itch-related quality of life measured by the Skindex-10 questionnaire. Other endpoints included safety, sleep quality, and additional measures including the 5-D itch scale.

Results: A significant reduction from baseline in itch intensity scores at week 8 favored all difelikefalin doses combined versus placebo ($P = 0.002$). Difelikefalin also showed improvement over placebo in Skindex-10, 5-D itch, and sleep disturbance scores ($P \leq 0.005$). Overall, 78% of patients receiving difelikefalin reported treatment-emergent adverse events versus 42% of patients given placebo, with diarrhea, dizziness, nausea, somnolence, and fall being the most frequent (≥5%).

Conclusion: In this trial, difelikefalin effectively reduced itching intensity and improved sleep and itch-related quality of life.

Kidney Int Rep (2020) **5,** 600–610; https://doi.org/10.1016/j.ekir.2020.01.006
KEYWORDS: chronic kidney disease; CKD-aP; CR845; hemodialysis; kappa opioid receptor agonist; uremic pruritus

See Commentary on Page 577

Patients with end-stage renal disease undergoing hemodialysis have a significantly shortened life expectancy and lower quality of life (QoL) compared with the general population.[1] Their QoL and life expectancy may be further reduced when they suffer from chronic kidney disease-associated pruritus (CKD-aP), also called uremic pruritus, a distressing complication of CKD characterized by generalized and persistent itching.[2–6] CKD-aP often leads to considerable mechanical skin damage, with excoriations, superimposed infections, and chronic lesions due to continuous and uncontrollable scratching.[7] This itching condition severely impacts mental and physical health, resulting in sleep disturbance, depressed mood, increased risk of infection, and a potential increased risk of mortality relative to hemodialysis patients without pruritus.[2]

There are no therapies for the treatment of CKD-aP that are approved by the Food and Drug

Correspondence: Frédérique Menzaghi, Cara Therapeutics, Inc., 4 Stamford Plaza, 107 Elm Street, 9th Floor, Stamford, Connecticut 06902, USA. E-mail: fmenzaghi@caratherapeutics.com
[7]Trial Investigators are listed in the Appendix.

Received 22 December 2019; accepted 13 January 2020; published online 28 January 2020

Administration or the European Medicines Agency, and this condition appears to be largely underrecognized.[8,9] Surveys indicate that >60% of hemodialysis patients have pruritus, with 20% to 40% being moderately to extremely bothered by itching,[10] despite improvements in dialysis techniques, use of emollients, increased duration of dialysis, use of phosphate binders, or use of vitamin D products. Several drugs approved for other indications are often used off-label; however, evidence for their antipruritic efficacy is either weak or these drugs are not always tolerated by patients. In the absence of strong data supporting the use of most treatments that are attempted in clinical practice, therapeutic options have been recommended, but without approved guidelines,[2,11,12] indicating a clear unmet medical need for this condition.

The pathogenesis of CKD-aP is not fully understood, but is thought to be multifactorial, including involvement of complex interactions between peripheral sensory neurons and immune cells.[13,14] Opioid receptors are known to modulate itch signals and kappa opioid receptor (KOR) signaling may suppress itch.[15–17] KORs are expressed on both central and peripheral cells,[14] and we hypothesized that activation of KORs on peripheral sensory neurons and on immune cells may be sufficient to suppress itch.

Difelikefalin (CR845) is a peripherally restricted and selective agonist at KORs, with no identified off-target activity.[18] Its unique all D-amino acid–based peptide structure is different from small organic heterocycle KOR agonists studied to date, which activate both central and peripheral KORs in addition to other receptors. Preclinical studies demonstrated that due to its physicochemical properties, difelikefalin does not penetrate the blood–brain barrier and thus may not produce the undesirable central nervous system effects related to activation of central KORs (e.g., dysphoria, hallucinations).[18] The concern for side effects commonly associated with mu opioid receptor agonists (which constitute most opioid analgesics) is also absent because difelikefalin does not bind to mu opioid receptors or any other receptors beside KORs.[18] Thus, it presents no risk for euphoria and respiratory depression in comparison with clinically used opioid analgesics (unpublished results). Difelikefalin reduces scratching behavior induced by chemically diverse pruritogens[17] and produces anti-inflammatory effects[18] in animal models. Difelikefalin is mostly renally excreted, resulting in a long half-life in hemodialysis patients ($t_{1/2} \approx 24$ hours) and clearance by dialysis (F. Menzaghi, unpublished data, 2019).

The present trial was designed to assess the safety and antipruritic effect of multiple doses of difelikefalin over 8 weeks of treatment in patients with moderate-to-severe CKD-aP undergoing hemodialysis.

METHODS

Study Population

This was a randomized, double-blind, placebo-controlled phase 2 trial (ClinicalTrials.gov: NCT02858726) to assess the efficacy and safety of difelikefalin over an 8-week treatment period in hemodialysis patients with moderate-to-severe pruritus to identify an optimal dose for chronic use. The study was conducted at 33 sites in the United States.

Key inclusion criteria were as follows: male or female adults ≥18 years; patients with end-stage renal disease who have been on hemodialysis 3 times per week for at least 3 months before screening; persistent pruritus during the month before screening, with weekly mean Worst Itching Intensity Numerical Rating Scale (WI-NRS) score over the 7 days before randomization >4 (scale of 0 [no itching] to 10 [worst itching imaginable]).[19] If the patient was using a stable treatment for itch , such as antihistamines, corticosteroids, topical treatments, gabapentin, or pregabalin for the past 14 days before screening, the regimen was maintained through the end of the treatment period. Exclusion criteria included use of opioid antagonists (e.g., naloxone, naltrexone) or opioid mixed agonist-antagonists (e.g., buprenorphine, nalbuphine) (see full inclusion and exclusion criteria in the Supplementary Material).

Procedures

Eligible patients were stratified according to their use or nonuse of antipruritic medications during the week before randomization, and randomized (1:1:1:1 ratio using a Web Response System) to receive an i.v. bolus of difelikefalin (0.5, 1.0, or 1.5 μg/kg) or placebo in isotonic acetate buffer (pH 4.5) at the end of each hemodialysis session for 8 weeks. Patients, investigators, clinical study site staff, and sponsor staff directly involved with the study were masked to treatment assignment throughout the trial. A follow-up visit was conducted approximately 1 week after the last dose (Figure 1).

Because pruritus is a sensation that can be reported only by patients themselves, complementary patient-reported outcome measures were used to assess the impact of difelikefalin on itch intensity and QoL. Patients were asked to report their WI-NRS score over the past 24 hours daily from the week before randomization (baseline) until the end of the treatment period. The WI-NRS is a validated 11-point scale that ranges from 0 to 10, with higher scores indicating worst itch intensity.[19] Itching severity scores collected via the WI-NRS have been categorized in the literature as mild (<4), moderate (≥4 to <7), or severe (≥7).[20] During

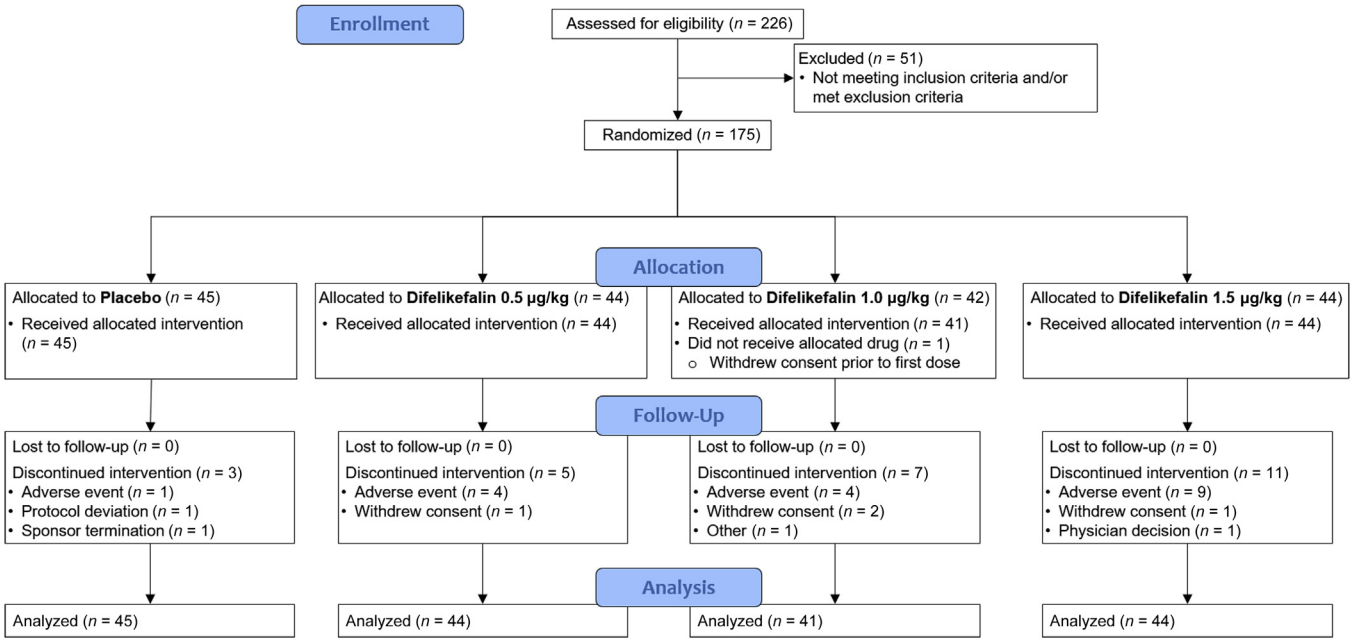

Figure 1. Patient disposition.

selected study visits, patients completed 5 additional patient-reported outcome questionnaires: the Skindex-10 Scale that assesses 3 domains related to itch (disease, mood/emotional distress, and social functioning)[19]; the 5-D itch scale that assesses 5 domains of itch and its impact (degree, duration, direction, body distribution of itch, and disability due to itch)[21]; the Medical Outcomes Study sleep disturbance scale[22]; the Patient Global Impression of Worst Itch Severity to assess itch severity by category (from none to very severe) over the past 24 hours[23]; and the Patient Global Impression of Change to assess overall changes in itch (improvement to worsening) since the start of the study.[24] All patient-reported outcomes were completed on paper before study drug administration at the dialysis center during hemodialysis sessions, except for the WI-NRS, which was also completed at home (at a similar time each day) on nondialysis days. Questionnaires were completed by each patient without any assistance.

Vital signs, 12-lead electrocardiogram data, and clinical laboratory tests were monitored periodically; adverse events were continuously recorded from the screening visit through the end of the follow-up period. A review of the unblinded aggregated safety data was conducted by an independently managed Data Safety Monitoring Board, which met twice during the study.

The study protocol was approved by the institutional review board or independent ethics committee for each study site. Written informed consent was obtained from all patients before screening. The study was conducted in accordance with the principles set forth in the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki, and no amendments were made to the original protocol.

Study Endpoints

The primary efficacy endpoint was the change from baseline at week 8 (end of treatment) in the weekly mean of the 24-hour daily WI-NRS score. Baseline was defined as the mean of the scores collected during the 7 days before randomization.

The secondary endpoint was the change from baseline at week 8 in the Skindex-10 total score. Other itch-related QoL endpoints included change from baseline at week 8 with respect to individual Skindex-10 domains, 5-D itch total score (and domains), and the Medical Outcomes Study sleep disturbance subscale. Baseline for QoL and sleep measures was defined as the value collected on the first day of administration of study drug before randomization.

Additional endpoints included the proportion of patients who rated their itch condition as *very much improved* or *much improved* as measured by the Patient Global Impression of Change at week 8 and the proportion of patients with a 1-category improvement from baseline on the Patient Global Impression of Worst Itch Severity at week 8. Safety was assessed based on reports of adverse events, clinical laboratory evaluations, vital signs, and electrocardiograms.

Statistical Analysis

A sample size of 40 patients per arm was deemed adequate to provide an appropriate estimate of the magnitude and variability of treatment effect at each

dose. Assuming an SD of 2.4, this sample size provided 80% power to detect a difference of 1.5 points between difelikefalin and placebo with respect to the weekly mean of the 24-hour WI-NRS with a 5% type I error.

The primary and secondary efficacy endpoints were analyzed using a mixed effects model with repeated measures,[25] using all visit weeks up to week 8 of treatment, including treatment, week, and treatment-by-week interaction as fixed effects, and prior antipruritic medication usage (yes/no) and baseline score as covariates. In the primary efficacy analysis, missing daily worst itching scores were not imputed. Assuming the data were missing at random, the estimates of the treatment differences calculated from the mixed effects model with repeated measures without imputation are unbiased. All pairwise comparisons against placebo were evaluated for each efficacy endpoint. In addition, a prespecified analysis of all difelikefalin doses combined against placebo was performed. There was no adjustment for multiplicity. Testing of hypotheses was 2-sided and the null hypothesis was rejected at a 5% type I error level. *Post hoc* analyses comparing the proportion of patients with a ≥3-point and a ≥4-point improvement from baseline between difelikefalin treatment groups and placebo were also performed. All efficacy analyses were conducted on the Full Analysis population (patients who received ≥1 dose, analyzed according to planned treatment arm), whereas analyses of safety data were performed on the safety population (patients who received ≥1 dose, analyzed according to actual treatment arm) using SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

The study was conducted between July 13, 2016, and March 14, 2017. Of the 226 hemodialysis patients screened, 174 patients from 33 US sites were allocated to 1 of 4 study arms to receive placebo or difelikefalin (0.5, 1.0, or 1.5 μg/kg) for 8 weeks thrice weekly after each hemodialysis (Figure 1).

The median age of randomized patients was 59 years, most were men (60%) and Black or African American (59%). Demographics and baseline characteristics were generally similar across study groups (Table 1). Medical conditions present in at least 30% of the patients in any treatment group are listed in Supplementary Table S1. Patients had been receiving hemodialysis for an average of 5.8 years and had chronic itching for 4.4 years (Table 1). Use of antipruritic medications at baseline was common (42%) (Table 1), and included mainly antihistamines and topical corticosteroids, with ≤2% of patients taking gabapentin.

Itch Intensity

The baseline itch intensity was calculated as the average of the WI-NRS score (scale of 0 [no itching] to 10 [worst itching imaginable]) recorded daily during the week before randomization. Scores ranged from 6.7 to 7.1 and were similar across treatment groups (Table 2).

A significant change from baseline at week 8 in WI-NRS score favored all difelikefalin doses combined compared with placebo (difference of −1.3 [95% confidence interval {CI}: −2.1 to −0.5]; $P = 0.002$), with an average decrease of −3.8 points (95% CI: −4.5 to −3.1) for the 0.5 μg/kg dose group, −2.8 (95% CI: −3.5 to −2.0) for the 1.0 μg/kg dose group, and −3.2 (95% CI: −3.9 to −2.4) for the 1.5 μg/kg dose group compared with −1.9 (95% CI: −2.6 to −1.3) for the placebo group (Figure 2a, Table 2). Patients randomized to 0.5 μg/kg and 1.5 μg/kg had statistically significant reductions in itch intensity compared with placebo ($P < 0.001$ and $P = 0.019$, respectively). The 1.0 μg/kg difelikefalin group showed a greater numerical reduction in WI-NRS score but the difference did not reach statistical significance ($P = 0.107$) (Figure 2a, Table 2). The effect of difelikefalin on itch intensity was evident starting at week 2 and further increased through the treatment period (Figure 2b), with no apparent dose response.

Overall, the weekly mean WI-NRS scores in the difelikefalin groups decreased from the moderate-to-severe to the mild itch category by the end of the study, whereas the weekly mean WI-NRS scores for the placebo group plateaued in the moderate itch category (Figure 2b). The efficacy of difelikefalin was similar in patients with or without background use of antipruritic medications (Figure 2c).

The proportion of patients with a ≥3 point improvement in the weekly mean WI-NRS score by week 8 was significantly higher with difelikefalin 0.5 μg/kg (64%; $P = 0.002$), 1.5 μg/kg (67%; $P = 0.002$), and the all difelikefalin combined group (59%; $P = 0.001$) compared with placebo (29%). The proportion of patients with a ≥4-point improvement in the weekly mean WI-NRS score by week 8 was significantly higher with difelikefalin 0.5 μg/kg (51%; $P = 0.014$) and the all difelikefalin combined group (44%; $P = 0.038$) compared with placebo (24%).

Itch-Related QoL and Sleep Quality

Patients in all difelikefalin treatment groups reported a significant improvement in itch-related QoL as measured by a reduction from baseline in the mean Skindex-10 total score at week 8 of −16.4 in all difelikefalin combined versus −8.2 in the placebo group ($P < 0.001$) (Figure 3a, Table 2). Significant

Table 1. Baseline demographics and clinical characteristics

Baseline demographics	Placebo ($n = 45$)	Difelikefalin 0.5 μg/kg ($n = 44$)	Difelikefalin 1.0 μg/kg ($n = 41$)	Difelikefalin 1.5 μg/kg ($n = 44$)	Total ($n = 174$)
Age, median (yr)	60.0	57.0	59.0	56.5	58.5
Range (minimum, maximum)	(27, 84)	(29, 80)	(26, 84)	(29, 74)	(26, 84)
Sex, male, *n* (%)	28 (62.2)	26 (59.1)	23 (56.1)	28 (63.6)	105 (60.3)
Race, *n* (%)					
Black or African American	25 (55.6)	24 (54.5)	22 (53.7)	31 (70.5)	102 (58.6)
White	16 (35.6)	17 (38.6)	19 (46.3)	10 (22.7)	62 (35.6)
Other (Asian, American Indian, Hawaiian or other Pacific Islander)	3 (6.7)	3 (6.8)	0	3 (6.8)	9 (5.2)
Not reported	1 (2.2)	0	0	0	1 (0.6)
Baseline dry weight (kg, post HD) (mean [SD])	81.0 (19.8)	83.5 (20.9)	85.4 (25.1)	82.8 (20.3)	83.1 (21.4)
Baseline clinical characteristics					
Patient-assessed disease severity, category C[a], *n* (%)	10 (22.2)	18 (40.9)	14 (34.1)	9 (20.5)	51 (29.3)
Duration of CKD-aP, yr (mean [SD])	4.4 (4.7)	4.7 (3.9)	4.6 (4.3)	3.9 (3.4)	4.4 (4.1)
Years since ESRD (mean [SD])	6.6 (5.4)	5.9 (4.9)	7.2 (4.9)	5.9 (4.6)	6.4 (5.0)
Years on chronic hemodialysis (mean [SD])	5.9 (4.9)	5.4 (4.9)	6.3 (4.7)	5.5 (4.4)	5.8 (4.7)
Most recent $spKt/V_{urea}$	$n = 43$	$n = 44$	$n = 39$	$n = 40$	$n = 166$
Mean (SD)	1.6 (0.3)	1.6 (0.2)	1.6 (0.3)	1.6 (0.3)	1.6 (0.3)
Most recent URR	$n = 8$	$n = 4$	$n = 9$	$n = 8$	$n = 29$
Mean (SD)	73.3 (4.6)	72.0 (3.9)	78.2 (6.6)	71.6 (3.0)	74.2 (5.4)
Etiology of CKD,[b] *n* (%)					
Diabetes	21 (46.7)	24 (54.5)	20 (48.8)	19 (43.2)	84 (48.3)
Hypertension and large-vessel disease	21 (46.7)	21 (47.7)	20 (48.8)	24 (54.5)	86 (49.4)
Glomerulonephritis/vasculitis	5 (11.1)	6 (13.6)	4 (9.8)	2 (4.5)	17 (9.8)
Other	1 (2.2)	2 (4.5)	3 (7.3)	2 (4.6)	8 (4.7)
Interstitial nephritis/ pyelonephritis	1 (2.2)	0	0	0	1 (0.6)
Cystic/hereditary/congenital disease	0	2 (4.5)	2 (4.9)	1 (2.3)	5 (2.9)
Urologic	0	0	1 (2.4)	0	1 (0.6)
Unknown	0	0	0	1 (2.3)	1 (0.6)
Blood chemistry (mean [SD])					
Calcium, mmol/l	2.2 (0.2)	2.1 (0.2)	2.2 (0.2)	2.2 (0.2)	2.2 (0.2)
Bilirubin, μmol/l	7.4 (2.1)	8.2 (3.5)	8.0 (4.0)	8.2 (4.1)	7.9 (3.5)
Phosphate, mmol/l	1.9 (0.5)	1.8 (0.7)	1.9 (0.6)	1.7 (0.5)	1.8 (0.6)
Hemoglobin, g/l	105.6 (11.0)	107.0 (11.4)	107.4 (13.9)	106.2 (10.5)	106.5 (11.6)
Parathyroid hormone, ng/l	478.6 (500.8)	314.4 (266.1)	389.3 (344.7)	353.7 (206.5)	384.9 (351.5)
Use of antipruritic medication,[c] *n* (%)					
Any prior anti-pruritic medication	18 (40.0)	20 (45.5)	17 (41.5)	18 (40.9)	73 (42.0)
Diphenhydramine hydrochloride	11 (24.4)	11 (25.0)	11 (26.8)	11 (25.0)	44 (25.3)
Hydroxyzine hydrochloride	2 (4.4)	6 (13.6)	2 (4.9)	3 (6.8)	13 (7.5)
Topical hydrocortisone	5 (11.1)	1 (2.3)	2 (4.9)	1 (2.3)	9 (5.2)

CKD, chronic kidney disease; CKD-aP, CKD-associated pruritis; ESRD, end-stage renal disease; HD, hemodialysis; Kt/V_{urea}, clearance of urea multiplied by dialysis duration and normalized for urea distribution volume; $spKt/V_{urea}$, single-pool Kt/V; URR, urea reduction ratio.
[a]Disease severity category C: I often have scratch marks on my skin that may or may not bleed or get infected; I often have a problem sleeping because of itching; my itching often makes me feel agitated or sad.
[b]More than 1 item may have been checked.
[c]Prior medications reported by ≥5% of patients in any treatment group. A patient reporting more than 1 medication for a particular medication name was counted only once for each medication name; prior medications included all medications that the patient had taken any time during the 14 d before the start of screening up until the first dose of study drug on day 1.

improvements were observed across all Skindex-10 domains, including disease severity (bothered by itching, persistence/reoccurrence of itching, and the appearance of skin from scratching) ($P \leq 0.009$ for all difelikefalin combined or individual dose groups), mood/emotional distress ($P \leq 0.010$ for all difelikefalin combined and 0.5 μg/kg), and social functioning ($P = 0.026$ to $P = 0.009$ for all difelikefalin combined or individual dose groups except for 1.5 μg/kg) (Supplementary Table S2).

Patients treated with difelikefalin also reported significant improvements from baseline in mean 5-D itch total scores compared with placebo at week 8, with a reduction of −5.3 in all difelikefalin combined versus −2.8 in the placebo group ($P < 0.001$) (Figure 3a, Table 2). For the 5-D scale domains, significant improvements from baseline at week 8 for difelikefalin versus placebo were observed for degree (intensity of itching) ($P = 0.044$ to $P < 0.001$, all difelikefalin combined or individual dose groups),

Table 2. Change from baseline at week 8 and responder rates for various efficacy outcomes

Endpoint	Placebo (n = 45)	Difelikefalin 0.5 μg/kg (n = 44)	Difelikefalin 1.0 μg/kg (n = 41)	Difelikefalin 1.5 μg/kg (n = 44)	Difelikefalin All difelikefalin combined (n = 129)
LS mean change from baseline and difference from placebo for change from baseline at week 8[a]					
Primary endpoint: weekly mean of daily 24-h Worst Itching Intensity NRS score					
Baseline (mean [SD])	6.8 (1.5)	7.1 (1.4)	6.7 (1.5)	6.7 (1.4)	6.8 (1.4)
LS mean change (SEM)	−1.9 (0.4)	−3.8 (0.4)	−2.8 (0.4)	−3.2 (0.4)	−3.2 (0.2)
95% CI	−2.6 to −1.3	−4.5 to −3.1	−3.5 to −2.0	−3.9 to −2.4	−3.7 to −2.8
Difference vs. placebo					
LS mean change (SEM)		−1.8 (0.5)	−0.8 (0.5)	−1.2 (0.5)	−1.3 (0.4)
95% CI		−2.8, −0.8	−1.9, 0.2	−2.3, −0.2	−2.1, −0.5
P value		<0.001	0.107	0.019	0.002
Secondary endpoint: Skindex-10 total score					
Baseline (mean [SD])	35.5 (12.4)	35.1 (13.4)	33.1 (11.7)	32.4 (12.4)	33.6 (12.5)
LS mean change (SEM)	−8.2 (2.0)	−18.7 (2.0)	−15.5 (2.2)	−15.1 (2.3)	−16.4 (1.3)
95% CI	−12.1 to −4.3	−22.7 to −14.6	−19.9 to −11.1	−19.6 to −10.5	−18.9 to −13.9
Difference vs. placebo					
LS mean change (SEM)		−10.4 (2.8)	−7.2 (3.0)	−6.8 (3.0)	−8.2 (2.3)
95% CI		−16.0 to −4.8	−13.1 to −1.4	−12.8 to −0.8	−12.8 to −3.5
P value		<0.001	0.016	0.026	<0.001
5-D itch total score					
Baseline (mean [SD])	17.2 (3.1)	17.3 (3.6)	16.6 (3.2)	16.4 (4.1)	16.8 (3.6)
LS mean change (SEM)	−2.8 (0.5)	−5.7 (0.5)	−5.4 (0.6)	−4.7 (0.6)	−5.3 (0.3)
95% CI	−3.8 to −1.7	−6.8 to −4.6	−6.6 to −4.3	−5.9 to −3.5	−5.9 to −4.6
Difference vs. placebo					
LS mean change (SEM)		−2.9 (0.8)	−2.7 (0.8)	−1.9 (0.8)	−2.5 (0.6)
95% CI		−4.4 to −1.5	−4.2 to −1.1	−3.5 to −0.4	−3.7 to −1.3
P value		<0.001	<0.001	0.016	<0.001
Itch MOS sleep disturbance score					
Baseline (mean [SD])	57.3 (24.5)	49.1 (25.0)	50.0 (21.2)	46.1 (23.2)	48.4 (23.1)
LS mean change (SEM)	−1.3 (3.1)	−13.8 (3.2)	−14.6 (3.4)	−6.9 (3.5)	−11.8 (2.0)
95% CI	−7.5 to 4.8	−20.0 to −7.5	−21.4 to −7.8	−13.9 to 0.1	−15.6 to −7.9
Difference vs. placebo					
LS mean change (SEM)		−12.4 (4.5)	−13.3 (4.7)	−5.6 (4.7)	−10.4 (3.7)
95% CI		−21.2 to −3.6	−22.5 to −4.1	−14.9 to 3.8	−17.7 to −3.1
P value		0.006	0.005	0.240	0.005
Responder rate at week 8, n (%)[b]					
PGIS	22 (52.4)	30 (76.9)	26 (74.3)	22 (66.7)	78 (72.9)
P value vs. placebo		0.036	0.061	0.244	0.021
PGIC	18 (41.9)	32 (78.0)	25 (62.5)	22 (56.4)	79 (65.8)
P value vs. placebo		<0.001	0.079	0.269	0.007

CI, confidence interval; LS, least-squares; MOS, Medical Outcomes Study; NRS, numerical rating scale; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Worst Itch Severity.
[a]LS means, SEMs, CIs, and P values are based on a mixed effects model with repeated measures analysis using all visit weeks up to week 8 of treatment, including treatment, week, and treatment-by-week interaction as fixed effects, prior antipruritic medication usage and baseline score as covariates. NRS values analyzed are the weekly means of the daily score; if a patient had >3 missing scores for the week, the week's mean was set to missing.
[b]For PGIS, patients were considered responders if they had a 1-point improvement from baseline; P values were based on Fisher's exact test. For PGIC, patients were considered responders if the response was *very much improved* or *much improved*; P values were based on Fisher's exact test.

duration of itching ($P = 0.019$ to $P = 0.003$, all difelikefalin combined or individual dose groups except 1.5 μg/kg), direction (better/worse in the preceding 4 weeks) ($P = 0.025$ to $P < 0.001$, all difelikefalin combined or individual dose groups), and disability (which includes effect of itch on sleep and activities related to leisure, housework/errands, and work/school) ($P \leq 0.008$, all difelikefalin combined or individual dose groups). Differences were not significant for the anatomical distribution domain (Supplementary Table S2).

Improvement in itch-related QoL measures were highly correlated with a reduction in the WI-NRS score at week 8, with a Pearson coefficient (r) of 0.67 and 0.71 for the Skindex-10 and 5-D itch total scores, respectively ($P < 0.0001$ for both comparisons) (Figure 3b).

As measured by the Medical Outcomes Study sleep disturbance questionnaire, the 0.5 μg/kg, 1.0 μg/kg, and all difelikefalin combined groups reported a significant reduction from baseline in sleep disturbance at week 8 compared with placebo ($P \leq 0.006$) (Table 2).

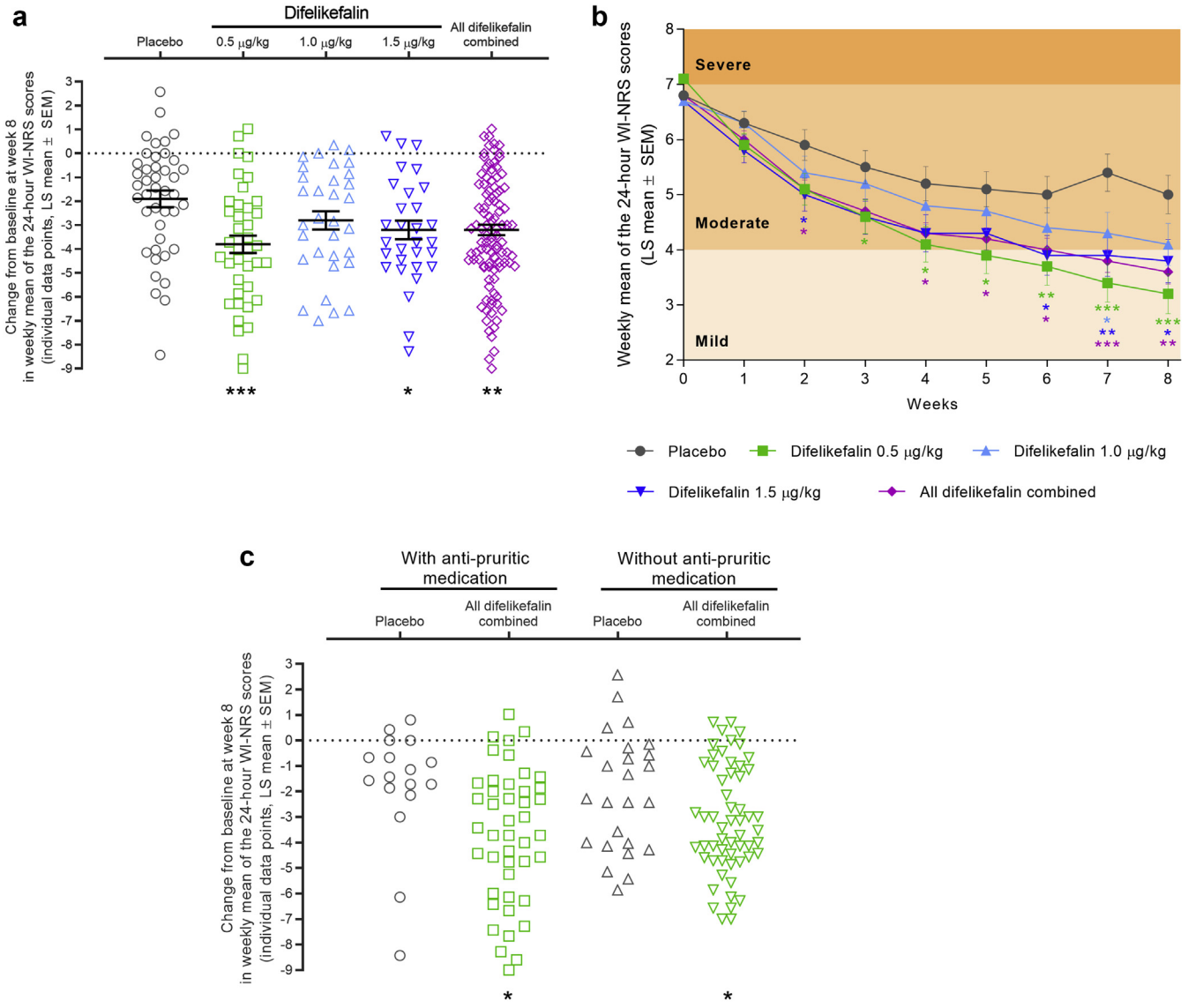

Figure 2. (a) Change from baseline at week 8 in the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores for difelikefalin versus placebo. (b) Weekly mean of daily 24-hour WI-NRS scores over 8 weeks for difelikefalin versus placebo. The shaded areas indicate the itch severity category based on the WI-NRS classification.[20] (c) Changes from baseline at week 8 in the weekly mean of the daily 24-hour WI-NRS score for difelikefalin (all difelikefalin doses combined) versus placebo according to baseline use or nonuse of antipruritic medications. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo (mixed effects model with repeated measures; see Statistical Analysis section), ($n = 41$–45/group). LS, least-squares.

The proportion of patients in the all difelikefalin combined group perceiving global improvement in itch severity by at least 1 category (i.e., severe to moderate; moderate to mild) was significantly higher (73%, compared with 52% in the placebo group; $P = 0.021$) (Table 2), with statistically significant differences versus placebo observed in the 0.5-μg/kg group ($P = 0.036$) (Table 2). The proportion of patients in the all difelikefalin combined group who reported their itch was *very much improved* or *much improved* was significantly higher (66% compared with 42% in the placebo group; $P = 0.007$) (Table 2, Figure 4). Similarly, significant differences versus placebo were observed in the 0.5-μg/kg group (78%; $P < 0.001$) (Table 2). Overall, 14% of placebo patients worsened, compared with 2% of difelikefalin patients (Figure 4).

Safety

Most treatment-emergent adverse events were classified as mild or moderate. Serious adverse events were most prevalent at the highest difelikefalin dose: placebo (4 of 45, 8.9%), 0.5 μg/kg difelikefalin group (10 of 44, 22.7%), 1.0 μg/kg difelikefalin group (6 of 41, 14.6%), 1.5 μg/kg difelikefalin group (11 of 44, 25.0%) (Supplementary Table S3). The most commonly reported serious adverse events were abdominal pain (3 patients; 6.8%) in the 0.5 μg/kg group and mental

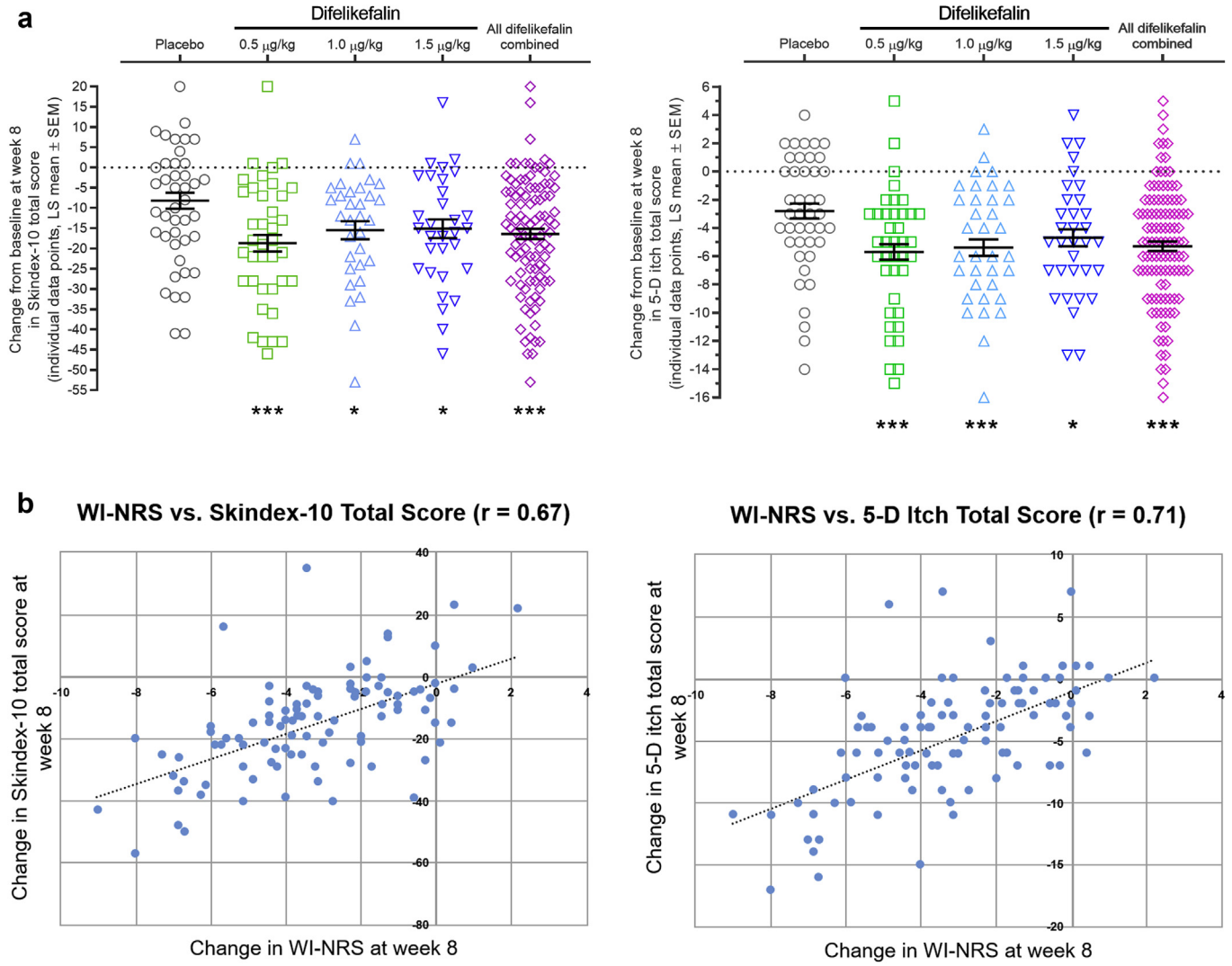

Figure 3. (a) Changes from baseline at week 8 in quality-of-life (QoL) measures for difelikefalin versus placebo as per Skindex-10 total score (left) and 5-D itch total score (right). (b) Correlation between changes from baseline for QoL measures and Worst Itching Intensity Numerical Rating Scale (WI-NRS) at week 8. *$P < 0.05$, ***$P < 0.001$ versus placebo based on a mixed effects model with repeated measures analysis, ($n = 41$–45/group). LS, least-squares; *r*, Pearson's correlation coefficient.

status changes (3 patients; 6.8%) in the 1.5 μg/kg group. The 3 patients with mental status changes had concomitant medical events, such as cerebral multifocal infarcts, a diphenhydramine overdose, and a case of hypertensive urgency, which were all considered unrelated to study drug. Four deaths occurred during the study: 1 case of respiratory failure (placebo group), 2 cases of cardiac arrest (1.5 μg/kg group), and 1 case of septic shock (0.5 μg/kg group); none of the deaths were considered related to study drug (Table 3).

Altogether, 78% and 42% of patients in the all difelikefalin combined and placebo groups, respectively, reported treatment-emergent adverse events (TEAEs) (Table 3). The most common (≥5%) TEAEs in the all difelikefalin combined group were diarrhea, dizziness, nausea, somnolence, and fall. Somnolence occurred at a low and similar rate (<5%) in the 2 lower-dose groups, but with higher incidence in the 1.5 μg/kg group (5 patients; 11.4%). Adverse events of mental status change were reported more frequently in the high-dose (1.5 μg/kg) group (11.4%) compared with the 1.0 μg/kg group (2.4%) and the 0.5 μg/kg group (0%). A dose-response trend was seen for TEAEs resulting in study drug discontinuation. Somnolence was the most commonly reported event that led to discontinuation (2 patients [4.5%] in the 1.5 μg/kg group). No events of dysphoria or euphoria were reported. No clinically relevant findings were observed with respect to laboratory, vital sign, or electrocardiogram results.

DISCUSSION

Chronic pruritus in patients undergoing hemodialysis represents a distressing medical condition with a significant unmet need. The current study demonstrates

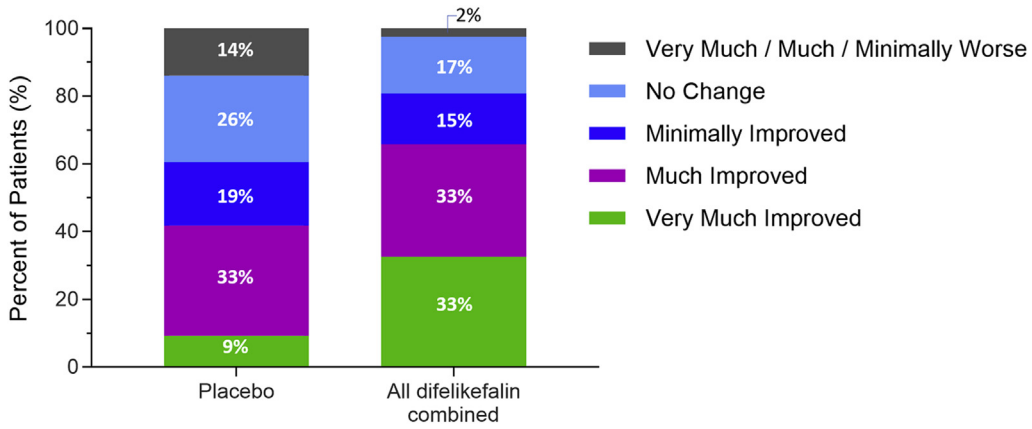

Figure 4. Percentage of patients per Patient Global Impression of Change categories on 8 weeks of exposure to all difelikefalin combined or placebo. For graphic representation, percentages were rounded to the nearest whole number.

that difelikefalin effectively reduced the intensity and duration of pruritus, improved sleep quality, and improved itch-related QoL, including mood/emotional distress, social functioning, and ability to perform daily activities, in hemodialysis patients with moderate-to-severe CKD-aP.

The effects on QoL measures are noteworthy, given that the level of disability and depressed mood in dialysis patients is high.[3] These findings are also significant because controlled trials of other interventions studied for CKD-aP on important sequelae of itching, such as impaired sleep and social and physical function, have not generally been reported.[26]

All 3 doses of difelikefalin reduced itching intensity compared with placebo (primary endpoint), regardless of whether the patients were taking other antipruritic medications. Therapeutic benefit was evident in the second week and itching continued to improve over time through the end of the treatment period. The proportion of patients reporting a reduction in itch intensity (WI-NRS) of ≥3 points by week 8 was significantly higher in the difelikefalin-treated groups compared with the placebo group. Based on a psychometric analysis of data from this study, improvement in WI-NRS of ≥3 points translates into a clinically meaningful change in itch for this patient

Table 3. Overall summary of treatment-emergent adverse events (TEAEs) and TEAEs reported by ≥5.0% of patients in any treatment group

	n (%) of patients				
		Difelikefalin			
Overall summary of TEAEs	Placebo (*n* = 45)	0.5 μg/kg (*n* = 44)	1.0 μg/kg (*n* = 41)	1.5 μg/kg (*n* = 44)	All difelikefalin combined (*n* = 129)
Any TEAE reported	19 (42.2)	37 (84.1)	29 (70.7)	34 (77.3)	100 (77.5)
Any serious TEAE reported	4 (8.9)	10 (22.7)	6 (14.6)	11 (25.0)	27 (20.9)
Any TEAE resulting in study drug discontinuation	1 (2.2)	4 (9.1)	4 (9.8)	7 (15.9)	15 (11.6)
Deaths	1 (2.2)	1 (2.3)	0	2 (4.5)	3 (2.3)
TEAE (preferred term) reported by ≥5% of patients in any group					
Diarrhea	0	7 (15.9)	4 (9.8)	5 (11.4)	16 (12.4)
Dizziness	2 (4.4)	6 (13.6)	4 (9.8)	2 (4.5)	12 (9.3)
Nausea	0	5 (11.4)	2 (4.9)	3 (6.8)	10 (7.8)
Somnolence	1 (2.2)	2 (4.5)	2 (4.9)	5 (11.4)	9 (7.0)
Fall	0	3 (6.8)	2 (4.9)	2 (4.5)	7 (5.4)
Abdominal pain	0	4 (9.1)	1 (2.4)	1 (2.3)	6 (4.7)
Hyperglycemia	0	3 (6.8)	1 (2.4)	2 (4.5)	6 (4.7)
Mental status changes	0	0	1 (2.4)	5 (11.4)	6 (4.7)
Paraesthesia	0	1 (2.3)	2 (4.9)	3 (6.8)	6 (4.7)
Fatigue	0	1 (2.3)	1 (2.4)	3 (6.8)	5 (3.9)
Headache	1 (2.2)	0	5 (12.2)	0	5 (3.9)
Hyperkalemia	0	3 (6.8)	1 (2.4)	1 (2.3)	5 (3.9)
Pruritus	0	3 (6.8)	1 (2.4)	1 (2.3)	5 (3.9)
Hypertension	0	0	1 (2.4)	3 (6.8)	4 (3.1)
Pulmonary edema	0	1 (2.3)	0	3 (6.8)	4 (3.1)
Anemia	3 (6.7)	0	1 (2.4)	0	1 (0.8)

population (unpublished results). Upon difelikefalin treatment, patients' mean itch scores moved from the moderate-to-severe to the mild itch severity category by the end of the study, whereas the mean WI-NRS scores for the placebo group plateaued in the moderate itch severity category, and significantly fewer difelikefalin-treated patients self-reported an itch of *very severe* and *severe* intensity. Itch intensity reduction correlated strongly with QoL improvement. This correlation, coupled with an improvement in sleep quality and categorical improvements in patient global assessment of itch severity and perception of change, underscores the clinical relevance of the reduction in itching observed in the difelikefalin-treated patients.

No clear dose response in relation to efficacy was observed, likely a result of the potency of difelikefalin and the exposure levels achieved at all doses due to the low rate of clearance in hemodialysis patients; however, a more favorable safety profile was observed for the 2 lower-dose groups compared with the high-dose group, and the most favorable benefit-risk profile appeared to be achieved with a difelikefalin dose of 0.5 μg/kg.

The safety profile of difelikefalin was consistent with findings across the development program including a recent phase 3 trial,[27] and reflects this patient population that presents with significant comorbidities. The most frequently (≥5%) reported TEAEs across all difelikefalin combined doses were diarrhea, dizziness, nausea, somnolence, and fall, and serious adverse events and discontinuations due to TEAEs were most prevalent in the 1.5 μg/kg group. The 3 deaths that occurred in the active study groups were all considered to be unrelated to study drug, and their causality is consistent with the fact that cardiovascular disease and sepsis are the leading causes of mortality in the hemodialysis patient population.[28]

The strengths of this study include allowance of background antipruritic medications that were ongoing before the study, which enabled the efficacy of difelikefalin to be evaluated in patients receiving treatments typically used in clinical practice. In addition, the clinical benefit of itch reduction was evaluated with multiple measures, with demonstration of high correlation between itch reduction and clinical QoL outcomes. Finally, it is worth noting that an i.v. formulation and thrice-weekly administration schedule is convenient and may assist with compliance in hemodialysis patients, who typically require numerous concomitant medications.

Design limitations of this trial include its relatively small sample size and lack of statistical adjustment for the comparisons of each active dose with placebo. The placebo response observed in this study (~30% improvement from baseline in WI-NRS scores) was consistent with that reported in other studies in comparable patient populations.[29–31] Nevertheless, the totality of the data and the consistency of the results across all efficacy analyses were sufficient to select 0.5 μg/kg as the preferred dose when considering the benefit-risk in this patient population, thus fulfilling the study objectives. This dose of difelikefalin was recently evaluated in a phase 3 trial in hemodialysis patients with pruritus over a 12-week treatment period.[27]

In conclusion, difelikefalin was effective at reducing the severity and duration of pruritus in hemodialysis patients with chronic moderate-to-severe CKD-aP, and improving sleep, mood, and social functioning. These data provide support for further investigation of the antipruritic effect of difelikefalin in larger and longer-term studies of the same population.

DATA SHARING

As a member of the Biotechnology Industry Organization (BIO), Cara will adhere to the BIO Principles of Clinical Trial Data Sharing.

APPENDIX

List of Trial Investigators

Michael Aaronson, Kelly Alford, Ahmed Awad, Premila Bhat, Varshab Broumand, Wesley Calhoun, Riad Darwish, Sohan Dua, Carl Dukes, Ayodele Erinle, Alexander Hadley, John Hsieh, Mohammad Kashif, Nelson Kopyt, Jayant Kumar, Jorge Kusnir, Jean Lee, Essam Maasarani, Richard Miller, M. Reza Mizani, Jesus Navarro, Amber Podoll, Thomas Pohlman, Denise Rivers, Derrick Robinson, Lisa Rich, Shayan Shirazian, Arnold Silva, Mark Smith, Joel Topf, James Tumlin, Scott Ungar, and Steven Zeig.

DISCLOSURE

CM, RHS, and FM are employed by Cara Therapeutics, Inc. SS attended a data release meeting and received travel expenses for attending this meeting. SB, MJG, and VM received fees from Cara for serving as medical consultants and/or medical monitors during the conduct of the study. SF was chair of the Data Safety Monitoring Board.

ACKNOWLEDGMENTS

The study was funded by Cara Therapeutics, Inc. The funders of the study contributed to the study design, data analysis, and preparation of tables and figures. All authors approved the final manuscript for publication. We thank the patients, the investigators, and the staff at the participating dialysis centers for their valuable contributions to the study. We are also grateful to Joana Goncalves and Joshua Cirulli from the sponsor for providing invaluable support with the publication process and critical review of

the manuscript content, and to Eric Justice, Alexandra Stirling, Kathryn Miles, and John Cooke from Bioscience Communications, New York, NY, for their medical writing and editorial support.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Appendix A. List of trial investigators.

Supplementary Appendix B. Trial enrollment criteria.

Table S1. Medical conditions present in ≥30% of patients in any treatment group at baseline.

Table S2. Itch-related quality-of-life subscale scores (change from baseline at week 8).

Table S3. Serious treatment-emergent adverse events.

REFERENCES

1. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chronic Kidney Dis*. 2007;14:82–99.
2. Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis*. 2017;10:11–26.
3. Ramakrishnan K, Bond TC, Claxton A, et al. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. *Int J Nephrol Renovasc Dis*. 2013;7:1–12.
4. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2006;21:3495–3505.
5. Narita I, Alchi B, Omori K, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int*. 2006;69:1626–1632.
6. Chen HY, Chiu YL, Hsu SP, et al. Elevated C-reactive protein level in hemodialysis patients with moderate/severe uremic pruritus: a potential mediator of high overall mortality. *QJM*. 2010;103:837–846.
7. Kuypers DR. Skin problems in chronic kidney disease. *Nat Clin Pract Nephrol*. 2009;5:157–170.
8. Hayani K, Weiss M, Weisshaar E. Clinical findings and provision of care in haemodialysis patients with chronic itch: new results from the German Epidemiological Haemodialysis Itch Study. *Acta Derm Venereol*. 2016;96:361–366.
9. Aresi G, Rayner HC, Hassan L, et al. Reasons for underreporting of uremic pruritus in people with chronic kidney disease: a qualitative study. *J Pain Symptom Manage*. 2019;58:578–585.
10. Rayner HC, Larkina M, Wang M, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol*. 2017;12:2000–2007.
11. Reszke R, Szepietowski JC. End-stage renal disease chronic itch and its management. *Dermatol Clin*. 2018;36:277–292.
12. Weisshaar E, Szepietowski JC, Dalgard FJ, et al. European S2k guideline on chronic pruritus. *Acta Derm Venereol*. 2019;99:469–506.
13. Kremer AE, Feramisco J, Reeh PW, et al. Receptors, cells and circuits involved in pruritus of systemic disorders. *Biochim Biophys Acta*. 2014;1842:869–892.
14. Snyder LM, Chiang MC, Loeza-Alcocer E, et al. Kappa opioid receptor distribution and function in primary afferents. *Neuron*. 2018;99:1274–1288.
15. Phan NQ, Lotts T, Antal A, et al. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: a literature review. *Acta Derm Venereol*. 2012;92:555–560.
16. Bigliardi PL, Bigliardi-Qi M. Peripheral opioids. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment*. Boca Raton (FL): CRC Press/Taylor & Francis; 2014:305–318.
17. Cowan A, Kehner GB, Inan S. Targeting itch with ligands selective for κ opioid receptors. *Handb Exp Pharmacol*. 2015;226:291–314.
18. Albert-Vartanian A, Boyd MR, Hall AL, et al. Will peripherally restricted kappa-opioid receptor agonists (pKORAs) relieve pain with less opioid adverse effects and abuse potential? *J Clin Pharm Ther*. 2016;41:371–382.
19. Mathur VS, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010;5:1410–1419.
20. Reich A, Heisig M, Phan NQ, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. *Acta Derm Venereol*. 2012;92:497–501.
21. Elman S, Hynan LS, Gabriel V, et al. The 5-D itch scale: a new measure of pruritus. *Br J Dermatol*. 2010;162:587–593.
22. Stewart AL, Ware JE, eds. *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach*. Durham, NC: Duke University Press, 1992.
23. Guy W. Clinical Global Impressions Scale (CGI). In: Rush AJ, ed. *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association; 2008.
24. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.
25. Mallinckrodt CH, Clark SW, Carroll RJ, et al. Assessing response profiles from incomplete longitudinal clinical study data under regulatory considerations. *J Biopharm Stat*. 2003;13:179–190.
26. Simonsen E, Komenda P, Lerner B, et al. Treatment of uremic pruritus: a systematic review. *Am J Kidney Dis*. 2017;70:638–655.
27. Fishbane S, Jamal A, Munera C, et al. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*. 2020;382:222–232.
28. United States Renal Data System. *2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
29. Wikström B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol*. 2005;16:3742–3747.
30. Razeghi E, Eskandari D, Ganji MR, et al. Gabapentin and uremic pruritus in hemodialysis patients. *Ren Fail*. 2009;31:85–90.
31. Mathur VS, Kumar J, Crawford PW, et al. A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. *Am J Nephrol*. 2017;46:450–458.